

Suharti *et al.*

# Characteristic Patients with Multiple Myeloma at Dr. Kariadi Hospital Semarang

Santosa Iva, Catharina Suharti, Mika Lumban Tobing, Suyono, Eko Adhi Pangarsa

Division of Hematology-Medical Oncology, Department of Internal Medicine,  
Diponegoro University-Dr. Kariadi Hospital Semarang

## ABSTRAK.

Latar belakang. Multiple myeloma (MM) adalah keganasan yang membedakan karakter B-limfosit ditandai dengan akumulasi sel plasma klon dalam sumsum tulang (BM), adanya imunoglobulin monoklonal (Ig) dalam serum atau urine, dan lesi tulang osteolitik.<sup>1</sup> Komplikasi penyakit ini terdiri dari infeksi bakteri berulang, anemia, lesi osteolitik dan penurunan fungsi ginjal.<sup>2-5</sup> MM adalah penyebab 1% kematian dari kematian akibat kanker di negara-negara Barat. Insiden MM adalah 1% dari semua keganasan dan 10% dari keganasan hematologi di ras Kaukasia dan 20% di ras Afro Amerika.<sup>2</sup>

Tujuan. Tujuan dari penelitian ini adalah untuk mengetahui data deskriptif karakteristik pasien dengan Multiple Myeloma di Rumah sakit dr. Kariadi Semarang.

Metode. Meskipun pembangunan di manajemen pasien, MM masih penyakit yang tak tersembuhkan, dengan tingkat ketahanan hidup 5 tahun lebih rendah dari 40%. Ada banyak perbedaan di myeloma dan manifestasi klinis. Beberapa pasien dapat bertahan di bulan sampai lebih dari 10 tahun.<sup>5,6,7</sup> Kelangsungan hidup rata-rata adalah 33 bulan, jumlah ini sama dalam studi Asia.<sup>8,9</sup>

Hasil. Ada beberapa faktor prognostik dalam manajemen myeloma, seperti  $\beta$ 2-mikroglobulin ( $\beta$ 2m), albumin serum, serum kreatinin, persentase sel plasma di sumsum, tulang litik lesi,  $\beta$ 2m anemia.<sup>10-13</sup> merupakan faktor prognostik yang digunakan oleh Sistem Staging Internasional (ISS)<sup>11</sup> untuk menentukan stadium dan prognosis di MM.  $\beta$ 2m berkorelasi dengan faktor-faktor lain, seperti kreatinin serum, anemia, mekanisme kerusakan tulang pada pasien MM.<sup>11,13</sup>

Kesimpulan. MM di Indonesia belum diteliti secara komprehensif sedangkan pengukuran  $\beta$ 2m mahal dan tidak tersedia secara luas.

**Kata kunci:** *Multiple Myeloma, Sumsum tulang, Prognosis Factors*

## ABSTRACT

Background. Multiple myeloma (MM) is a malignancy of differentiated B-lymphocytes characterized by accumulation of clonal plasma cells in the bone marrow (BM), the presence of a monoclonal immunoglobulin (Ig) in the serum and/or urine, and osteolytic bone lesions.<sup>1</sup> Complications of this disease consist of recurrent bacterial infection, anemia, osteolytic lesion and decreased renal function.<sup>2-5</sup> MM is the cause of death in 1% of cancer death in Western countries. MM incidence is 1% of all malignancies and 10% of hematologic malignancies in Caucasian race and 20% in the Afro American race.<sup>2</sup>

**Aim.** The aim of the study is to know the descriptive data of characteristic of patients with MM at dr. Kariadi Hospital Semarang.

**Metode.** Despite of development in patient management, MM is still an incurable disease, with 5-year survival rates lower than 40%. There are many differences in myeloma and its clinical manifestations. Some patients can survive in the months until over than 10 years.<sup>5,6,7</sup> The median survival was 33 months, this number is similar in Asian studies.<sup>8,9</sup>

**Results.** There are several prognostic factors in myeloma management, such as  $\beta_2$ -Microglobulin ( $\beta_2m$ ), serum albumin, serum creatinine, plasma cell percentage in marrow, bone lytic lesion, anemia.<sup>10-13</sup>  $\beta_2m$  is a prognostic factor used by the International Staging System (ISS)<sup>11</sup> to determine stadium and prognosis in MM.  $\beta_2m$  correlates with other prognostic factors, such as serum creatinine, anemia, mechanism of bone destruction in MM patients.<sup>11, 13</sup>

**Conclusion.** MM in Indonesia has not been studied comprehensively and the  $\beta_2m$  measurement is expensive and not widely available.

**Keywords:** *Multiple Meyloma, bone marron, prognostic factors*

## MATERIAL AND METHOD

This is a cross sectional study. The design and conduct of the study complied with the principles of good clinical practice, in accordance with the Declaration of Helsinki. The study was approved by local ethics committees and written informed consent was obtained from all patients before enrollment. The patients are older than 14 years old, who are new and old patients diagnosed with MM that referred to dr. Kariadi Hospital Semarang.

Patients were evaluated for physical examination, laboratory measurement, and bone survey. Complete blood count was analyzed using ABX Micros 60<sup>®</sup>. Creatinine serum was measured from blood clot using Gas-chromatography-isotope dilution mass spectral method. Albumin serum was measured using Bromocresol green method. Beta-microglobulin was analyzed using Enzyme-linked immunosorbent assays (ELISA) method. Immunofixation was analyzed using the Hellabio Immunofixation Electrophoresis (IFE).

## Data Analysis

Data were analyzed using SPSS 12 evaluation version. The data showed as descriptive method.

## RESULTS

### Demographic Characteristic

Between January and December 2010, 25 patients with clinical diagnosis of MM were included in this study. The demographic characteristics were shown in Table 1. Median age was 56 (SE  $\pm 1.8$ ). The study population was mostly men (79%). Private employee, government employee, farmer, entrepreneur, and others were 13 patients (52%), 7 patients (28%), 2 patients (8%), 2 patients (8%), and 1 patient (4%), respectively. The main complaint was bone pain, this occurred in 15 patients (60%), followed by shortness of breath in 4 patients (16%), swelling of shoulder in 1 patient (4%), forehead tumor in 1 patient (4%), petechiae in 1 patient (4%), fatigue in 1 patient (4%), weakness in 1 patient (4%), bone pain in 1 patient (4%), and bone fracture in 1 patient (4%).

Laboratory characterizations were shown in Table 2. The majority of patients have anemia with mean Hb level of 9.4 g/dL (SD  $\pm 2.7$ ). Leukocyte and Platelet counts were normal, 7.4 g/dL (SD  $\pm 2.9$ ) and  $200.3 \times 10^3 / \text{mm}^3$  (SD  $\pm 124$ ) respectively. The mean creatinine level was 1.7 mmol/L (SD  $\pm 1.1$ ). There was hypoalbuminemia with mean albumin level of 2.6 g/dL (SD  $\pm 0.6$ ), hyperglobulinemia with mean globulin level of 6.9 g/dL (SD  $\pm 1.8$ ) and normal calcium level with a mean of 2.3 mmol/L (SD  $\pm 0.4$ ). The mean  $\beta_2m$  level was 9.6 g/dL (SD  $\pm 8.9$ ).

**Table 1. The demographic data of 25 patients with MM**

Characteristic	All patient (N= 25)
Age at diagnosis, year *	56 (1.8)
Sex, Man/Woman (%)	76/24
Occupation (%)	
Farmer	2 (8)
Government employee	7 (28)
Private employee	13 (52)
Entrepreneur	2 (8)
Others	1 (4)
Main complaint (%)	
Shoulder swelling	1 (4)
Tumor in forehead	1 (4)
Ecchymosis	1 (4)
Fatigue	1 (4)
Weakness	1 (4)
Bone pain	15 (60)
Bone fracture	1 (4)
Shortness of breath	4 (16)
Complication (%)	
Fracture	4 (16)
Recurrent infection	5 (20)
Renal failure	1 (4)
Bleeding	1 (4)
Thrombosis	1 (4)
Neuropathy	2 (12)
Compression fracture of column vertebra	10 (40)
History of the past treatment (%)	
No treatment	13 (52)
With treatment	12 (48)
Duric-Salmon staging (%)	
I	0
II	1 (4)
IIIA/IIIB	24 (96)
International System Staging (ISS)	
I	4 (16)
II	5 (20)
III	16 (64)
*Median , (SE Median)	

The most complication in patients with MM is fracture; compression of lumbar vertebra 10 cases (40%) and fracture another site 4 cases (16%). According to Durrie Salmon staging system, 96% patients have stage III A/IIIB. However, according to the International staging system, 64% patients have stage III.

According to immunoisotype, total case of IgG  $\kappa$ , IgA  $\kappa$ , IgA  $\lambda$ , biclonal  $\lambda$  light chain and IgG  $\lambda$  were 11 patients (44%), 2 patients

(8%), 1 patient (4%), and 1 patient (4%), respectively. Thirty six (36%) patients have not been classified. The Bone survey examination showed that most of the patients have bone lytic lesion, 21 patients (88%).

**Table 2. The Laboratory data of patient with Multiple myeloma**

Variable	Mean ( $\pm$ SD)
Hemoglobine, gr/dL	9.4 $\pm$ 2.7
Leucocyte x 103/mm <sup>3</sup>	7.4 $\pm$ 2.9
Platelet x103/mm <sup>3</sup>	200.3 $\pm$ 124
Creatinine, mmol/L	1.7 $\pm$ 1.1
Albumin, g/dL	2.6 $\pm$ 0.6
Globulin, g/dL	6.9 $\pm$ 1.8
Calcium, mmol/L	2.3 $\pm$ 0.4
$\beta_2$ m, mg/dL	9.6 $\pm$ 8.9

**Table 3. Patient clasification with MM based on monoclonal protein**

Immunoisotype	total (%)
IgG $\kappa$	11 (44)
IgA $\kappa$	2 (8)
IgA $\lambda$ s	1 (4)
Biclonal $\lambda$ light chain and IgG $\kappa$	1 (4)
Light-chain $\kappa$	1 (4)
Not classified	9 (36)

**Table 4. Osteolytic Lesion of patient with MM**

Number of osteolytic bone, %	Total (%)
0 (no osteolytic)	4 (12)
1	1 (4)
2	12 (48)
3	4 (16)
4	2 (8)
5	1 (4)
6	0
7	1 (4)

## DISCUSSION

The median age of this study population was 56 years. Median age in a study in Taiwan was 62 years.<sup>14</sup> Median age in Royal Free Myeloma Clinic study was 67 years for

men, and 63 years for women.<sup>15</sup> Median age, according to Dispezieri (2009) was 71 years.<sup>5</sup> Median age of Kariyawan CC study (2007),<sup>16</sup> was 66 years. The median age in our study was lower than other studies. Man to woman ratio was 3.1: 1, this number is similar to the studies in other countries. The incidence of patients with MM was higher in men than in women, this result similar to another study.<sup>5, 17</sup>

Bone pain was the main complaint of MM patients in this study, 60%. In a study by Kariyawan CC, et al (2007),<sup>17</sup> 56% patients experienced bone pain ranging from mild, moderate, to severe. Bone involvement rather than symptomatic bone pain, bone lytic lesion and/or severe osteoporosis were the main features in patients with MM.<sup>18</sup>

Other complaints were swelling, tumor mass, petechiae, fatigue, fracture and sort of breath. Bone swelling and bone mass were caused by bone destruction. When a solitary mass appeared, this bone mass was called plasmacytoma.<sup>19,20</sup>

The complication of infection is usually found in MM patients. Patients with MM have decreased of immunity that resulted in susceptibility to infection. Disturbance in humoral immunity and leucopenia make patients with MM prone to infection. Patients with multiple myeloma were more susceptible to bacterial infections, especially from encapsulated microorganisms, such as pneumococcus, as well as a viral infection.<sup>21</sup> The study in Japan revealed that patients with MM have risk of bacterial infection include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli*. Sulfamethoxazole – trimethoprim oral for at least the first 2 months of chemotherapy were important prophylaxis for bacterial infection.<sup>22</sup>

Hypercalcemia was due to bone destruction in MM. Bone destruction mechanism and

disability of osteoblast to repair bone lesions in clinical remission phase have been understood.<sup>23</sup> Incidence of hypercalcemia in patients with MM was 20%, however all of the patient in this study have no hypercalcemia.

Most of the patients with MM came to hospital in advanced stage. According to Durrie Salmon staging system, 96% patients have stage III A or IIIB. However, according to the international staging system, 64% patients have stage III. These were caused by delay diagnosis and referral. Many patients came to a Neurologist, Nephrologist, and Orthopedist. Diagnosing MM in early stage is difficult, as shown in the result of this study; we should have more awareness in patients with bone pain.

The study in Taiwan revealed a correlation between farming exposure and MM. However, in this study, almost all of the population were private employees that have no farming exposure. There are many risk factors for MM. Although there were correlations between toxin, dietary source, environment pollution and increasing MM incidence, these findings still need epidemiology analysis in the future.<sup>14</sup>

All patients in this study have anemia. Anemia in patients with MM is anemia of chronic disease that caused by blunting of response to erythropoietin (EPO) and disorder of iron metabolism.<sup>24</sup>

This study has some limitations, because there were no analysis of parameters such as performance status, C reactive protein, chromosome 13 abnormalities, and plasma cell labeling index (PCLI).

## CONCLUSION

The characteristic data of patient with MM at dr. Kariadi Hospital similar to other

center. Almost the patient came to the hospital with advanced stage, bone complication, infection etc. There, interest data was the age patients with MM were younger than another center.

## REFERENCES

1. Drach J, Kaufmann H. New developments and treatment in multiple myeloma: new insights on molecular biology. ESMO 2002.
2. Bataille R, Harousseau JL. Multiple myeloma. *N Engl J Med*. 1997; 336 : 1657-1664.
3. Anderson KC, Kyle RA, Dalton. WS, et. al. Multiple myeloma: new insights and therapeutic approaches. *Hematology* 2002:147-165.
4. Dave SS, Dunbar CE. Multiple myeloma. In: Rodgers GP, Young NS. *Bethesda handbook of clinical hematology*. Philadelphia. Lippincott Williams & Wilkins. 2005: 221-231.
5. Dispenzieri A, Lancy MQ, Greipp PR. Multiple Myeloma. In: Greer JP, Foerster J, Rodger GM, et al. Editor, *Wintrobe 's clinical hematology*, 12<sup>th</sup> Edition. Philidalphia, Lippincott Williams & Wilkins. 2009: 2372-2438.
6. Barillé-Nion S, Barlogie, Bataille R, et al. Advances in biology and therapy of multiple myeloma. *Hematology* 2003: 248-278.
7. Decaux O, Lodé L, Minvielle S, Avet-Loiseau H. Genetic abnormalities in multiple myeloma: role in oncogenesis and impact on survival. [Pubmed: 17559979 ]
8. Kyle RA, Gertz MA, Witzif TE, et. al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003; 78:21-33.
9. Zhong Fei, . Wei-jun FU, Zhen-gang Y et al. Prognostic factors and staging systems of multiple myeloma. *Chinese Medical Journal* 2007;119(19) :1689-1693.
10. Greipp PR, Katzmman JA, O'Fallon WM, Kyle RA .Value of  $\beta$ 2-microglobulin level and plasma cell labeling indices as prognostic factors in patients with newly diagnosed myeloma. *Blood* 1988:219-223.
11. Greipp PR, Miguel JS, Durie BGM et al. International staging system for multiple myeloma. *J Clin Oncol* 2005: 2(15);3412-3420.
12. ultiple Myeloma: A practical guide to current management. The American School of Oncology. 2005.
13. Sharma S,Nemeth E, Chen YH, et al. Involvement of hepcidin in the anemia of multiple myeloma. *Clin Cancer Res* 2008;14; 3262-3267.
14. HuangSY,Yao M,TangJL et al.Epidemiology of Multiple Myeloma in Taiwan, Increasing Incidence for the Past 25 Years and Higher Prevalence of Extramedullary Myeloma in Patients Younger Than 55 Years. *Cancer* 2007; 110:896-905.
15. Free royal myeloma clinic
16. Kariyawan CC, Hughes DA, Jayatillake MM, Mehta AB. Multiple myeloma: causes and consequences of delay in diagnosis. *Q J Med* 2007; 100:635–640.
17. Zhong-fei T, Wei-jun F, Zhen-gang Y TAO Zhong-fei, FU Wei-jun, YUAN Zhen-ganget al. Prognostic factors and staging systems of multiple myeloma: a single center study in China. *Chin Med J* 2007;120(19):1655-1658

18. Rajkumar SV, Kyle RA. Multiple Myeloma: Diagnosis and Treatment. *Mayo Clin Proc.* 2005;80(10):1371-1382.
19. Bladé J, Rosiñol L. Moving forward in myeloma research. *Haematologica* 2004; 89(5):
20. United Kingdom Myeloma Forum. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. *British Journal of Haematology* 2004; 124: 717–726.
21. Grethlein SJ. Multiple Myeloma. <http://emedicine.medscape.com/article/204369-print>
22. Yoshida M. Compromised immune function in multiple myeloma. *Nippon Rinsho.* 2007 Dec;65(12):2238-42 [Abstract, Pubmed]
23. Roodman GD. Mechanisms of bone resorption in myeloma. *J Musculoskel Neuron Interact* 2003; 3(4):271-272.
24. Birgegård G. Managing anemia in lymphoma and multiple myeloma. *Therapeutics and Clinical Risk Management* 2008;4(2): 527-539.